A Current Approach to Hyperprolactinemia

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Abstract
Prolactin is a hormone secreted by the anterior pituitary lactotrophs and is controlled by the influence of hypothalamic dopamine. PRL stimulates the proliferation and differentiation of mammary cells for lactation. There are many causes for hyperprolactinemia, including analytical, physiological, pharmacological, pathological and idiopathic causes. Macroprolactin is a significant analytical cause of hyperprolactinemia, and the most common cause of pathological hyperprolactinemia is prolactin secreting adenomas. Symptoms of true hyperprolactinemia include galactorrhoea, secondary amenorrhea, oligomenorrhea and hypogonadotropic hypogonadism. Larger macroadenomas can cause compressive symptoms on the pituitary gland or visual symptoms. A single measurement of serum PRL obtained at any time of the day can be used to diagnose hyperprolactinemia. Macroprolactinemia should be excluded in all cases of hyperprolactinemia, and polyethylene glycol precipitation is a fast, convenient and inexpensive method to exclude macroprolactinemia. Other interferents that can cause falsely low prolactin readings include the hook effect, biotin and heterophilic antibodies. Physicians must know how to approach hyperPRL and exclude the most important differential diagnoses of prolactinomas.

Keywords
Prolactin, Hyperprolactinemia, Macroprolactinemia, Prolactinomas, PEG

Introduction
Prolactin (PRL) is a hormone synthesized and secreted by the anterior pituitary lactotrophs. This process is influenced by multiple stimulatory and inhibitory factors, the chief of which is dopamine [1]. Normally, dopamine from the hypothalamic arcuate nucleus acts on specific lactotroph dopamine receptors (D2) and inhibits pituitary PRL secretion [2]. The D2 receptor gene is located on chromosome 11. PRL is encoded by a single gene, located on chromosome 6 in humans [3]. Following its production pre-PRL (227 amino acids) is cleaved to form PRL (199 amino acids), a 23 kDa protein [4]. Extra-pituitary PRL has also been reported. Pituitary and extra-pituitary PRL have identical structures and bind PRL-R but the mechanisms of their regulation differ and are being elucidated [5]. Prolactin has strong structural homology with growth hormone and placental lactogen [6]. PRL is involved in the control of lactation. Post-partum, PRL stimulates the differentiation and proliferation on mammary cells that has been primed for lactation by other hormones - estrogen, progesterone, insulin, corticosteroids and Growth Hormone (GH). The large increase in PRL during lactation is associated with a decreased dopamine output, mediated by a decrease in the phosphorylation of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis [7]. During lactation, the increase in PRL is accompanied by the proliferation and hypertrophy of lactotrophs in the pituitary gland [8]. Even after lactation with a return of dopamine inhibition, the hypertrophy of the lactotrophs persists for several months, allowing for higher PRL levels with subsequent lactation [2].
Besides the 23 kDa PRL monomer (‘little PRL’) other PRL isoforms are present in the circulation. These macromolecular complexes of PRL and IgG autoantibodies are ‘big PRL’ (48-56 kDa) and ‘big big PRL’ (> 150 kDa), a polymer referred to as macroprolactin (macro-PRL) [9]. In normal subjects, total circulating prolactin comprises 65-85% little PRL, 10-20% big prolactin, and < 10% big big prolactin [10]. Macro-PRL has minimal biological activity and pathological function but is variably detected in the current PRL immunoassays. The large size of macroPRL results in lower renal clearance and this elevates the total PRL without any increase in lactotroph PRL release. This phenomenon, also called “analytical hyperprolactinemia”, can lead to misinterpretation of PRL results. Proteolytic cleavage of the active 23kDa PRL protein produces 14kDa, 16kDa and 22kDa PRL variants [4]. There has been increasing interest in the role of the 16kDa fragment of prolactin in angiogenesis. It uses plasminogen activator inhibitor-1 as a binding partner to activate the urokinase-type plasminogen activator receptor [11,12] which inhibits angiogenesis [13]. This 16kDa PRL variant may have roles in peripartum cardiomyopathy [14] and preeclampsia [15].

PRL acts via its membrane receptor, the Prolactin Receptor (PRL-R), the gene for which is located on chromosome 5 [16]. PRL-R (598 amino acids) is formed from the cleavage of pre-PRL-R (622 amino acids). PRL-R is a member of the class 1 hematopoietic cytokine receptor superfamily that includes GH [17]. The structure of the PRL-R has now been elucidated and the mechanism of its activation deciphered [2]. Human PRL-R binds 3 ligands (PRL, GH, and placental lactogen) rendering it difficult to ascertain the specific effects of PRL in vivo [18]. The PRL-R, initially thought to be restricted to lactating cells, has been now found to be widespread in the body including in adipose tissue, skin and hair follicles, pancreas, bone and adrenal glands [19]. In the pancreas, it regulates the ontogenesis of pancreatic stem cells to create a functional reserve of beta cells [20] that may contribute to beta-cell proliferation during pregnancy.

The pituitary gland is an anatomic meshwork of differentiated cells with great plasticity that enables formation of new differentiated cell types in response to new signals and inputs [21]. Control of pituitary function is complex and finely integrated through three tiered loops - the hypothalamus, intrapituitary signals, and peripheral hormone feedback [22]. This complex regulation results in production of sufficiently abundant and appropriately timed regulatory secretions in response to external cues [23].

### Measurement of Serum Prolactin

Current automated immunoassays employed in clinical laboratories use a two-site immunometric or sandwich assay principle. Prolactin in the sample reacts with a capture antibody immobilised on a solid phase and a labelled detection antibody. Following capture of the analyte-antibody sandwich, unreacted reagents are washed away. The signal generated is directly proportional to the sample prolactin concentration. These modern immunometric assays are free from cross-reactivity of related molecules such as growth hormone and placental lactogen. Interference from heterophilic antibodies are also very rarely encountered as such assays have been optimised with blocking agents. However, interference from macro-PRL remains common. Most of the PRL assays are standardised to the World Health Organisation’s third international prolactin standard 84/500, which consists of the 23 kDa little PRL derived from human pituitaries. However, despite general concordance between PRL methods, agreement of PRL results from different vendors is still poor and PRL reference intervals are platform specific. The expected serum PRL concentration in normal adult males and females is less than 14 ug/L and 24 ug/L respectively (PRL conversion units: 1 ug/L = 21.2 mU/L). The reported reference ranges for total PRL on the Abbott Architect assay is 2.7-19.7 ug/L for males and 3.0-26.4 ug/L for females [24]. Serum PRL is unaffected by food and a fasting sample is not necessary [25].

### Causes of Hyperprolactinemia

The causes of hyperprolactinemia (hyperPRL) are listed in Table 1. The prevalence of hyperPRL is about 10 per 100,000 in men and 30 per 100,000 in women, respectively and it is the second most common cause of infertility in women after Polycystic Ovarian Syndrome (PCOS) [25].

<table>
<thead>
<tr>
<th>Causes of Hyperprolactinemia</th>
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<tbody>
<tr>
<td>1. Analytical (e.g. Macroprolactinemia)</td>
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<td>2. Physiological</td>
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<td>a. Pregnancy</td>
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<td>b. Lactation</td>
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<td>c. Stress</td>
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<td>3. Pharmacological</td>
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<td>a. Anti-psychotics (e.g. risperidone)</td>
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<td>b. Anti-hypertensives (e.g. verapamil)</td>
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<td>c. Anti-depressants (e.g. tricyclic antidepressants)</td>
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<td>d. Anti-epileptic drugs</td>
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<td>e. Metoclopramide</td>
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<td>f. Opiates</td>
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<td>g. Estrogens (e.g. oral contraceptives)</td>
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<td>4. Pathological</td>
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<td>a. PRL secreting adenomas</td>
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<tr>
<td>b. Hypothalamic/pituitary stalk disorders (e.g. granulomatous disease, irradiation, trauma)</td>
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<tr>
<td>c. Renal dysfunction</td>
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<td>d. Hepatic failure</td>
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<td>e. Hypothyroidism</td>
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<td>f. Hereditary disorders</td>
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<td>5. Idiopathic</td>
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Analytical HyperPRL or MacroPRL

MacroPRL is a significant analytical cause of hyperPRL with a prevalence of between 12.5-40% in hyperPRL patients [26-28]. Contemporary PRL immunoassays are not able to discriminate macroPRL from monomeric PRL. Immunoassays often utilize a “sandwich” assay where a capture and a labelled antibody bind to different segments of the PRL molecule to generate a signal that is directly proportional to the amount of serum PRL. MacroPRL can still bind extensively with these antibodies and generate a high intensity signal for PRL despite not being biologically active. MacroPRL increases with age, is stimulated by dopamine antagonists and responds to the physiologic stimuli that would normally increase PRL [9]. MacroPRL does not result in symptoms of hyperPRL. In fact, a recent study reported no evidence of hyperPRL symptoms in any of the 51 patients with macroPRL after a 10-year follow-up [29]. Although macroPRL is not of direct clinical significance, it may lead to misdiagnosis and injudicious management if not well understood [30]. MacroPRL can co-exist with true hyperPRL. In a study of 61 women with macroPRL and menstrual disturbances 59% had concomitant elevation of monomeric PRL after PEG precipitation [31]. Seemingly innocuous, laboratorians and clinicians need to be cognizant of the importance of macroPRL and hyperPRL [32]. Misdiagnosis can be avoided if the laboratory pretreats the serum sample with Polyethylene Glycol (PEG) to precipitate any macroprolactin before measuring prolactin [16].

Physiologic HyperPRL

There are physiologic causes for a rise in PRL such as pregnancy, lactation, physical exertion or stress. During pregnancy PRL increases in response to increasing estriol ranging from 35-600 ug/L [33]. PRL is not increased in non-lactating women and men after nipple stimulation or breast imaging and breast examination [34,35].

Pharmacologic HyperPRL

A variety of drugs (neuroleptics, antipsychotics e.g. risperidone, antidepressants, opiates, estrogens and metoclopramide) can cause hyperPRL [36]. Serum PRL is typically between 25-100 ug/L with the exception of risperidone where PRL levels up to 200 ug/L may be encountered [37]. A detailed drug history and a repeat PRL test after abstaining from the offending drug will exclude them as the cause of hyperPRL.

Pathologic HyperPRL

In Chronic Kidney Disease (CKD) PRL is elevated due to decreased clearance and increased secretion [38]. Some hypothyroid patients may have enlarged pituitary gland due to thyrotroph and/or lactotroph hyperplasia [39]. With treatment of hypothyroidism PRL values normalize. Among the most disconcerting causes of pathological hyperPRL are PRL secreting adenomas (prolactinomas) and hypothalamic/pituitary stalk disorders (including granulomatous disease, irradiation and trauma).

Prolactinomas account for up to 50% of the cases of hyperPRL [40]. The prevalence of pituitary adenoma ranges from 1/865-1/2688 in the general population [41] with 40-46% of these being prolactinomas [25,42]. Prolactinomas are more commonly encountered in women [43]. Prolactinomas may be classified by size. Microadenomas (< 10 mm) account for over 90% of cases [41]. Macroadenomas are over > 10 mm in size but may be greater than 40 mm (giant macroadenomas). PRL levels generally correspond to the tumour mass. Pituitary macroadenomas are typically associated with PRL levels > 250 ug/L [44]. In giant macroadenomas PRL may reach up to > 1000 ug/L [45]. The Endocrine Society highlights that PRL levels > 500 ug/L are highly suspicious of macroadenomas [25]. In a study by Vilari (n = 250) [40] the PRL levels in macroadenomas ranged from 100-500 ug/L, but in only 35% of them was PRL > 500 ug/L. As such, it is difficult to judge the size of prolactinomas based on PRL values alone. Larger prolactinomas can cause gonadotropin insufficiency from its compressive effects on the pituitary gland.

Most prolactinomas are sporadic. Occasionally, they occur as part of the rare hereditary disorders e.g. multiple endocrine neoplasia type 1 [46], Carney complex, or familial isolated macroprolactinoma [47]. Almost all prolactinomas are benign, but rarely they can be malignant and metastasize [48]. Ectopic prolactin secretion can also occur with ovarian dermoids or bronchogenic carcinoma [2].

Idiopathic HyperPRL

In some patients with PRL between 20-100 ug/L no cause can be identified although they may have microadenomas not visible on imaging. These cases are classified as idiopathic [49]. Familial cases of idiopathic hyperPRL have also been reported [50] from inactivating mutations in the PRL receptor. However, clinical manifestations of hyperPRL in these subjects were not manifest suggesting that loss-of-function mutation in the PRL receptor may result in inactive PRL isoforms or PRL insensitivity.

Evaluation of Hyperprolactinemia

Symptoms

Symptoms of true hyperPRL include galactorrhea, secondary amenorrhea, oligomenorrhea and anovulatory infertility. While galactorrhea is the classic symptom of hyperPRL, it only occurs in less than half of such cases [51]. HyperPRL inhibits neurons that release kisspeptin-1 [2,52]. These neurons stimulate neurons in the hypothalamus to release Go-
nadiotropin-Releasing Hormone (GnRH). Thus, hyper-PRL prevents GnRH and FSH/LH release resulting in hypogonadotropic hypogonadism. HyperPRL can also decrease estrogen levels through effects on ovarian aromatase activity and by blocking the stimulatory effects of FSH, as well as inhibit progesterone production [53]. HyperPRL in amenorrheic women with oestrogen deficiency aggravates osteoporosis. As PRL-R is present in bone [19], it is unclear if the low BMD is due to hyperPRL or the low gonadotropins associated with hyperPRL. Larger adenomas cause gonadotropin insufficiency from its compressive effects on the pituitary gland. In men, hyperPRL can lead to hypogonadism, decreased libido, erectile dysfunction, infertility, gynecomastia and galactorrhea. Men often present with macroadenomas associated with visual symptoms and headaches, not just due to a diagnostic delay but also because males develop more aggressive tumors [54]. Males are thus at greater risk of hypopituitarism at diagnosis, with the gonadal and somatotropic axes more frequently affected than thyrotropic and corticotropic axes [55].

**Investigations**

Dynamic testing for PRL is not useful in the investigation of hyperPRL and is no longer recommended by the Endocrine Society [25]. For suspected hyperPRL, the Endocrine Society recommends a single measurement of serum PRL obtained at any time of the day [25]. Pregnancy should be excluded in women of child-bearing age since prolactinomas can co-exist with pregnancy. Besides, the stimulating effect of placental estrogens on pituitary adenomas can lead to local compressive symptoms [53]. Renal or liver impairment, hypothyroidism, and concomitant use of drugs that can cause hyperPRL should be ruled out. In amenorrheic women, Follicle-Stimulating Hormone (FSH), Luteinising Hormone (LH) and/or Anti-Mullerian Hormone (AMH) should also be assessed to exclude ovarian failure/polycystic ovarian syndrome [25]. Magnetic resonance imaging (MRI) should be performed to visualize pituitary/sellar masses, followed by biopsy for histological diagnosis. In males with hyperPRL, testosterone levels should also be evaluated. In addition, patients should also be assessed for acromegaly, as mixed-cell adenomas secreting prolactin and Growth Hormone (GH) can occur [56]. Typically, acromegalic patients only have a moderate degree of hyperPRL, with some studies showing PRL levels of 131.3 ± 76.6 µg/L [57].

**Macroprolactinemia**

MacropRL should be assessed in all hyperPRL samples. Size Exclusion Chromatography (SEC) remains the gold standard for confirming macropRL, but it is labor intensive and impractical for regular laboratory use. An alternative common laboratory method is to use PEG precipitation, which is fast, convenient, and inexpensive. PEG solution is added to the plasma sample, mixed together, and centrifuged. MacropRL and other macro-molecular PRLs are precipitated (PEG-precipitable PRL) and monomeric PRL measured on the supernatant (free PRL). Total PRL is measured on an unmanipulated sample. The amount of macropRL is calculated thus:

\[
\text{Total PRL} - \text{free PRL} / \text{Total PRL} \%
\]

To diagnose macropRL a PEG-precipitation ratio of > 60% or a post-PEG PRL recovery (free PRL/Total PRL) < 40% is used.

Despite the expediency of PEG precipitation, there is large variability in the diagnostic criteria for the presence of macropRL after PEG precipitation. Different studies [6,27,31] use different percentage PRL recovery cut-offs to diagnose the presence of macropRL. Others [58] consider any decrease in PRL post-PEG treatment to be diagnostic. However, these percentage thresholds are arbitrary definitions and patients with recoveries below diagnostic cutoffs may still have true hyperPRL or macropRL. It has been suggested that PEG recoveries of 30-65% be classified as indeterminate, requiring further analysis with other methods (e.g. SEC) to diagnose macropRL. There are many different PEG precipitation protocols [59] with multiple sources of variation from sample volumes required, type of PEG used, PEG reconstitution methods, time of mixing, sample incubation and centrifugation time/temperature. This creates different recovery rates between laboratories and assays, which may further complicate the interpretation of PEG precipitation results as different amounts of true PRL are co-precipitated with the macropRL depending on the PEG protocol.

Although macropRL is not bioactive, non-specific symptoms of hyperPRL may still be present due to coincident elevation of PRL. If macropRL is not recognized, it can lead to misdiagnosis and mismanagement of hyperPRL. In a study of 337 patients with hyperPRL [60], 88 patients (26%) were found to have macropRL. Some patients with macropRL (n = 11) had abnormal pituitary MRI findings. In another study of 61 women with macropRL and menstrual disturbances [31], 59% had concomitant elevation of monomeric PRL after PEG precipitation and 36% of such patients had a pituitary abnormality on MRI imaging.

MacropRL is a common occurrence in patients with hyperPRL. Contemporary PRL immunoassays are not able to discriminate macropRL from monomeric PRL. There is also variation in PRL results on different assay platforms, particularly at higher concentrations of PRL, even after attempts at standardization with international reference materials. Different PRL assays vary in their ability to detect macropRL: ranging from between 2.3 to 7.8-fold difference [61] between the highest and lowest estimates. In our hospital, we have performed an analysis for macropRL between...
two assays (Abbott Architect and Roche Cobas e602) [62]. Sixteen percent (100/616) of the PRL requests were hyperPRL. The Architect PRL identified 18 subjects as macroPRL (18%) while the Cobas PRL identified 12 subjects (12%) although there was a 100% concordance of macroPRL between the 2 assays. It is thus preferable to monitor hyperPRL subjects using the same assay platform each time.

Most laboratories report results post-PEG precipitation as the percentage total prolactin recovered. However, this approach lacks diagnostic specificity especially when there is an excess of macroprolactin and monomeric prolactin at the same time. Thus, some studies have advocated the reporting of absolute PRL values with a modified PRL reference interval post-PEG precipitation to identify specimens with true hyperPRL after diagnosis of macroPRL [9,63-65]. PRL reference intervals post-PEG treatment need to be assay specific and should be derived with normal samples similarly treated with PEG. Ideally larger populations can be used so that confidence intervals for reference intervals can be established. There are also rare instances of spurious results post PEG treatment, for example, elevated GGT levels can cause increased precipitation of monomeric PRL and a false-positive macroPRL result [9], whereas macroPRL containing IgA may not precipitate and give a false-negative result [66]. Non-IgG-type macroPRL may be significant sometimes as some studies [67] have reported a prevalence of up to 32.3% of some patients with macroPRL. This may account, in part, for the variability in the sensitivity of different assays to macroPRL.

To better screen for macroPRL with PEG precipitation, several strategies can be employed. The first strategy is to assess for macroPRL only in asymptomatic patients with hyperPRL [25]. The second strategy is PEG precipitation in those patients with moderately elevated PRL without identifiable cause [44]. The third strategy is all hyperPRL sera are screened for macroPRL [9,68]. We favour the reflex screening for macroPRL with PEG precipitation in all hyperPRL samples to save time, costs and inconvenience for the patient. Another approach is to use a level of PRL where we can confidently rule out the presence of macroPRL. This was also discussed in the latest AACE guidelines on macroPRL [28]. While the guideline recommends testing asymptomatic patients with elevated PRL, they cite a study [69] where PRL levels were 350-400 ug/L in a patient with macroPRL. Considering the large variation in amounts of macroPRL between hyperPRL patients, the guidelines had no recommendation for a level of PRL at which macroPRL testing can be safely omitted.

Other prolactin assay pitfalls

The hook effect is a factor which can affect PRL analysis. In patients with giant pituitary adenomas, significantly high levels of PRL molecules saturate the antibodies of the sandwich assay, with signalling antibodies binding directly to excess PRL without capture antibodies, leading to results that are lower than expected [70]. This is an uncommon phenomenon that occurs in giant prolactinomas where the actual PRL levels can be as high as 1000-100,000 ug/L but are reported as 20-200 ug/L [45]. The hook effect is important because the PRL levels are used to decide upon surgical or medical management in these giant prolactinomas. The hook effect can be overcome by serial dilution of serum specimens; a serial dilution to 1:100 is recommended particularly in male patients with a moderate PRL elevation [25].

Biotin is another interferent that can affect PRL readings. Some automated immunoassays that incorporate biotin to label the capture antigen/antibody or the signal antibody are vulnerable. High serum biotin prevents the formation of biotin-antigen-antibody complexes, resulting in a falsely low signal and reading. However, such an aberrant PRL result depend on the amount of biotin intake. Biotin is also excreted by the kidneys, and their levels can increase in patients with renal dysfunction. Biotin levels in over-the-counter supplements are low (30-300 ug) and will not cause any assay interference. In one study [71] where samples were spiked with biotin, PRL readings only started to show significant decreases when biotin concentrations approached 500 ug/L, a level only seen with high-dose biotin therapy (100-300 mg/d) for multiple sclerosis. At serum biotin concentrations of 500 ug/L, the PRL decreased to 30.8-33.1% of baseline values. However, the prevalence of patients on significantly high levels of biotin is low. In a Mayo clinic study [72], only 2 out of 1944 emergency department patients had serum biotin concentrations > 100 ug/L (both patients had end stage renal disease).

Heterophilic or human anti-mouse antibodies can occasionally affect PRL readings in a biotin-like fashion [73]. No assay is completely fool proof and interferences should be considered when the PRL result is discordant with the clinical picture [74]. Care should also be taken in patients with autoimmune disease receiving antibody treatment, as many of these exogenous antibodies can induce the development of heterophilic/human anti-mouse antibodies in these patients [74]. If antibodies are suspected, reanalysing the sample with an alternative method, serial dilution, antibody precipitation or antibody-blocking tubes can help to reduce the interference and provide a more accurate result.

If all investigations prove negative, the hyperPRL can be deemed idiopathic [75]. Such cases may be autoimmune in nature, as evidenced by the presence of anti-pituitary antibodies in some patients [76].

Conclusion

In conclusion, physicians must know how to ap-
proach hyperPRL and exclude the most important dif-
ferential diagnoses of prolactinomas. They must be
aware of macroPRL. Detection of macroPRL with PEG is
straightforward but not fool proof. All hyperPRL sera
should be screened for macroPRL. Patients with hyper-
PRL can also be affected by the hook effect, biotin, or
other interferents.

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